Novel synthesis of biocompatible ultrasmall gold nanoparticles as sonosensitisers for sonodynamic therapy of breast cancer

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Gold nanoparticles (AuNPs) have previously shown promising potential as sonosensitisers for sonodynamic cancer therapy.[1] However, their clinical application is hindered by long term retention and toxicity in liver and spleen.[2] Ultrasmall AuNPs (usAuNPs; diameter <5 nm) have a potential to circumvent drawbacks of large AuNPs due to their increased rate of glomerular filtration as well as better tumour tissue penetration and higher rate of cancer cell uptake.[3-4] However, current methods of synthesizing usAuNPs either use toxic stabilising agents (E.g., CTAB, Tween 80, dodecanethiol) that undermine their clinical safety, or biocompatible macromolecules (E.g., reduced bovine serum albumin, folic acid) that ultimately increase average sizes of resulting usAuNPs beyond renal filtration threshold (>5nm), limiting their *in vivo* application. In this study, we developed a facile and rapid method to synthesise usAuNPs using sodium alginate as stabiliser. The alginate-stabilised usAuNPs ($usAuNPs^{ALG}$) showed an average hydrodynamic diameter of 4.5 (± 0.2) nm, a zeta potential of –30.4 (± 5.3) mV, and were physically stable in PBS and DMEM for up to 7 days. The $usAuNPs^{ALG}$ showed good haemocompatibility and cytocompatibility (L929 and 4T1 cell lines) for up to 100 µg/ml. Moreover, $usAuNPs^{ALG}$ acted as sonosensitisers, generating reactive oxygen species under ultrasound treatment, and induced dose-dependent sonotoxicity in 4T1 cells *in vitro* at low ultrasound power (0.5 W/cm^2), with comparable efficiency to the previously reported work for larger AuNPs exposed to 2 to 4-fold higher ultrasound power (1–2 W/cm^2). Overall, this study presented a facile synthesis of biocompatible usAuNPs and suggested their potential as sonosensitisers for sonodynamic therapy of breast cancer.

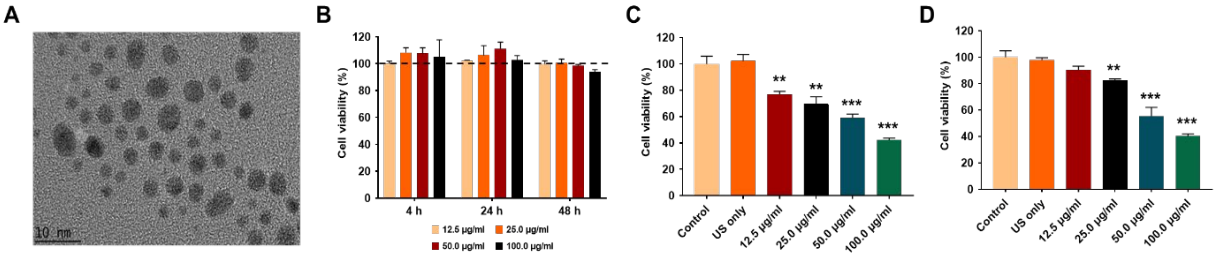

Figure 1: (A) TEM image of usAuNPs. **(B)** Cytotoxicity of usAuNPs in 4T1. Dose-dependent sonotoxicity of usAuNPs in **(C)** 4T1 and **(D)** MDA-MB-231 under ultrasound irradiation (1 MHz; 0.5 W/cm^2; 100% duty cycle, 3 min). Data is represented as mean ± SD (n=3). ** - p<0.01, *** - p<0.001, obtained by one-way ANOVA.

References:

[1] Brazzale, C. et al., Nanomedicine, **2016**, 12, 3053-3070.
[2] Fraga, S. et al., Nanomedicine: Nanotechnology, Biology and Medicine, **2014**, 10, 1757-1766.
[3] Naz, F. et al., Journal of drug targeting, **2016**, 24, 720-729.
[4] Huang, K. et al., ACS Nano, **2012**, 6, 4483-4493.